A full copy of the presentation will be available to meeting participants. This text includes key points to consider in diagnosing variants of hepatocellular carcinoma that show clear-cell change, fibrosis, or glandular/pseudoglandular architecture.

**Background**

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and the third most common cause of cancer-related deaths. In the liver, carcinoma is the end result of progression through dysplasia as follows:

- **Dysplastic foci** (cytologically atypical, less than 1 mm in diameter, identified incidentally)
- **Dysplastic nodules** (cytologically and/or structurally atypical), further subdivided into low-grade and high-grade

Cirrhosis is a significant risk factor for development of HCC, but non-cirrhotic liver also may form HCC, sometimes from malignant transformation of hepatocellular adenoma (such as the recently recognized subtype with beta-catenin mutation).

For nodules over 1 cm, the differential includes:

- Large regenerative nodule
- Focal nodular hyperplasia-like nodule, including hepatocellular adenoma
- Dysplastic nodule (>1 cm but <3 cm)
- **HCC** – including early HCC, classic HCC, and variants of HCC

**Classic HCC**

In order to approach key variants of HCC, the subject of this presentation, it is important to address characteristic features of well-differentiated HCC. On needle core biopsy, only some of these features may be seen, so close correlation with imaging findings, rate of growth of the lesion, and other clinical information is important:

- Proliferation of hepatocytes arranged in expanded plates (trabeculae, at least 3 cells thick) and/or acinar/pseudoglandular groups. Compact or solid areas may be present.
- Lack of normal portal tracts
- Increased arterialization within lesion
- Bile production
- Loss of reticulin staining or intact reticulin outlining irregular architectural groupings of lesional hepatocytes

When material is limited, the most useful stain as an adjunct to a good H&E stain is a reticulin stain. Additional unstained sections can be obtained at the time of initial
sectioning to avoid unnecessary loss of tissue. Serum increase in serum alpha-fetoprotein (AFP) is, in the UCSF experience, not highly sensitive or specific for the presence of HCC, and immunostaining for AFP is not pursued due to its low sensitivity, especially in small nodules of HCC.

**HCC with clear-cell change**

This is a relatively common variant that poses a diagnostic challenge, as it resembles other epithelioid tumors. HCC with fatty change falls into this category (generally small, early-stage tumors) as does HCC with steatohepatitis-like change (hepatocyte ballooning, formation of Mallory-Denk bodies).

The main challenge is constructing and exploring the differential, especially if the background liver is non-cirrhotic (as can happen with HCC) and especially if tissue is limited on biopsy. The differential of clear-cell tumors in the liver includes metastatic renal cell carcinoma (RCC), metastatic adrenocortical carcinoma, neuroendocrine carcinoma with clear-cell features, melanoma ("balloon cell" melanoma), epithelioid angiomyolipoma (AML), and mesenchymal tumors with epithelioid morphology including epithelioid GIST.

**Role of immunostains:** Specifically within tumors of clear-cell morphology, immunohistochemistry for Hep Par 1 (hepatocyte antigen) and MOC31 (epithelial cell adhesion molecule or EPCAM) will sort these possibilities as follows:

<table>
<thead>
<tr>
<th>Expression pattern</th>
<th>Leading considerations with clear-cell morphology</th>
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<tbody>
<tr>
<td>Hep Par 1 diffuse+ MOC31-</td>
<td>HCC</td>
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</tbody>
</table>
| Hep Par 1- MOC31+ | • Neuroendocrine tumor  
• RCC  
• Hep Par 1-negative HCC with aberrant MOC31 (rare) |
| Hep Par 1+ MOC31+ | None with classically clear-cell appearance, but adenocarcinomas with aberrant Hep Par 1 such as lung and gastroesophageal tumors may stain this way |
| Hep Par 1- MOC31- | Keratin+  
• Neuroendocrine tumor  
• RCC  
• Epithelioid GIST (rarely keratin-positive) |
**HCCs with a component of fibrosis**

The presence of fibrosis within HCC raises a complex differential including fibrolamellar carcinoma (FLM), scirrhou HCC, cirrhosis-like HCC, and combined HCC-cholangiocarcinoma).

**Fibrolamellar HCC (FLM)**

In contrast to most HCC, FLM typically occurs in non-cirrhotic liver in young adults (mean age, 26 years) and is not associated with any known risk factors. This is an aggressive tumor with a 5-year survival of 50-60%. Many studies have reported that FLM has a better outcome than conventional HCC as a whole, but this is likely to be related to the absence of cirrhosis in FLM, as cirrhosis is a significant adverse factor in HCC. The outcome of FLM is likely to be similar to that of conventional HCC arising in non-cirrhotic liver.

It is important to distinguish FLM and conventional HCC as extended hepatic resection and lymph node dissection are more often performed in FLM. Unresectable FLM may be treated with chemotherapy and radiation, possibly becoming amenable to resection after platinum-based chemotherapy.

A triad of morphological features should be adhered to strictly for the diagnosis of FLM:

- large polygonal tumor cells with abundant eosinophilic granular cytoplasm
- prominent macronucleoli
- lamellar fibrosis

Cytoplasmic granularity is due to the presence of numerous mitochondria. Tumor cells also contain “pale bodies” composed of fibrinogen and/or albumin. Pale bodies are not specific to FLM, as they can be seen in other types of HCC, including scirrhou HCC.

**Role of immunostains:** FLMs express markers of hepatocellular differentiation like Hep Par 1 and polyclonal CEA (canalicular pattern). AFP expression is absent in FLM, though rare cases may show focal expression in a few tumor cells (and this stain is not routinely used at UCSF in HCC workup). Glypican-3 is expressed in two-thirds of FLM compared to 80% of conventional HCC, while CK7 is expressed in nearly 80% of FLM compared to 20-30% of conventional HCC. CD68 is highly
sensitive for FLM and shows cytoplasmic positivity in a granular, dot-like, or stippled pattern (see Ross et al).

Diffuse staining with chromogranin or synaptophysin strongly favors a neuroendocrine tumor, as these markers are generally negative or only focally positive in most FLMs. Hepatocellular markers like Hep Par 1 and polyclonal CEA (canalicular pattern) are consistently negative in neuroendocrine tumors.

**Scirrhous HCC**

Scirrhous HCC is a distinct entity that is not the same as fibrolamellar carcinoma; the scirrhous pattern accounts for about 5% of all HCC, and most cases contain background cirrhosis. This tumor may be mistaken for cholangiocarcinoma on imaging; the hallmark of scirrhous HCC is abundant dense fibrosis admixed with the malignant hepatocytes that are generally organized into trabeculae, pseudoacinar structures, or solid nests. Most of the tumors originate just below the liver capsule, and some multifocal tumors may show areas of classic HCC. The pattern of fibrosis resembles that seen after treatment (chemotherapy, radiation, or transarterial chemoembolization).

The literature contains conflicting reports as to the prognosis of scirrhous HCC in comparison to classic HCC.

*Role of immunostains:* Hep Par 1 has only 50% sensitivity for this variant, and MOC31 expression may be more common (UCSF observations). Use of arginase, polyclonal CEA (canalicular pattern), and glypican-3 (GPC-3) as additional hepatocellular markers is helpful. Scirrhous HCC may express CK7 or CK19, possibly associated with poorer prognosis.

**Cirrhosis-like HCC**

Rare patients with cirrhosis have multifocal HCC with small cirrhosis-like nodules. Individual tumor cells resemble conventional HCC, but their growth pattern is unusual. Generally there is no mass seen on imaging. This is an insidious tumor as it often is not clinically suspected and may only be identified incidentally on a staging biopsy, in an explant, or at autopsy. Grossly, small cirrhosis-like tumor nodules are present and in some cases appear distinct from adjacent background cirrhotic nodules in color. Microscopically, tumor tends to be well- or moderately-differentiated, often with ballooning, Mallory-Denk bodies, and cholestasis.

Presence of small foci of HCC on multiple needle cores from a single biopsy procedure may increase suspicion for cirrhosis-like HCC. Sometimes cirrhosis-like HCC may co-exist with a dominant nodule of classic/conventional HCC. This is an evolving topic, and it remains unknown whether prognosis after transplantation is any different from that of conventional HCC.

*Role of immunostains:* No specific utility. A good reticulin stain is helpful to identify foci of HCC. Correlation with gross findings is important to make this diagnosis.
**Combined HCC-cholangiocarcinoma**

Though combined tumors are rare, they may show fibrosis. Combined HCC-cholangiocarcinoma is discussed in more detail below.

**HCC with pseudoglandular architecture**

The main differential here, particularly on needle core biopsy, is pseudoglandular HCC versus HCC-cholangiocarcinoma or a pure cholangiocarcinoma. In comparison to malignant glandular tumors, HCC has a relative lack of desmoplastic stroma. This pattern of HCC does not exhibit mucin production. There is no consensus on defining a CC component within combined HCC-CC, but the presence of intracytoplasmic or luminal mucin is compelling evidence for a CC component.

Per WHO criteria, combined HCC-CC contains closely mixed elements of HCC and CC showing appropriate phenotypic properties of each individual tumor. This type of combined HCC-CC comprises less than 1% of all HCC, may be more aggressive than either HCC or CC alone, and may show portal or hepatic vein invasion or lymph node metastasis at the time of presentation. Per the 1985 classification of Goodman et al., there are three subtypes:

- **Type I** – collision tumor with apparently coincidental HCC and CC in the same liver
- **Type II** – transitional tumor with elements of HCC closely associated and apparently transitioning to elements of CC
- **Type III** – fibrolamellar type, resembles fibrolamellar HCC but with mucin-producing pseudoglands

A recent case series from UCSF identified mixed HCC-cholangiocarcinoma or intrahepatic cholangiocarcinoma in the explants of 14 patients who underwent liver transplant for HCC (see Sapisochin et al). These patients had a high tumor recurrence rate (8/14 after a 32-month median follow-up).

**Role of immunostains:** Areas of hepatocellular origin will be highlighted by Hep Par 1 and arginase, while MOC31 and CK19 or CK7 can be helpful to identify cholangiolar components. However, CK19/CK7 should not be relied upon to make the diagnosis, as the biopsy could represent HCC with CK19/CK7 expression; this phenotype may be seen in noncirrhotic livers, and this expression pattern is associated with a poorer prognosis.

**Useful references**

**General and HCC with clear-cell change**


Zhou X, Yearsley MM, Jones K, Frankel WL. Hepatocellular carcinomas occasionally express neuroendocrine markers while neuroendocrine tumors metastatic to the liver do not show hepatocellular expression. Mod Pathol. 2011;24(Suppl 1):378A.

**Fibrolamellar HCC**


**Cirrhosis-like HCC**

**Scirrhouss HCC**

**Combined HCC-cholangiocarcinoma**
